REMARKS

Claims 1-10 were pending in the present application. Claims 1-8 have been amended and Claim 9 has been canceled herein. New claims 12-17 have been added herein. Support for the amended and new claims can be found throughout the specification and original claims. No new matter has been added. Upon entry of the present amendment, Claims 1-8, 10, and 12-17 will be pending.

I. Objections

Applicants' disclosure has been objected to because it is alleged that structural representations described therein are inconsistent with accepted practices of structure drawing in organic chemistry, and that all non carbon bonded hydrogens must be shown in order to avoid ambiguity. Applicants respectfully disagree and assert that such an amendment is unnecessary; as it is generally presumed that the proper valence will be attributed to each atom automatically. However, solely in order to expedite prosecution, the specification has been amended accordingly.

II. The Claimed Invention is Not Indefinite

Claim 9 has been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. *See* Office Action at page 3. Applicants have canceled Claim 9 herein, rendering the claim rejection moot.

III. The Claimed Invention is Enabled

Claims 1-7

Claims 1-7 have been rejected under 35 U.S.C. § 112, first paragraph, for allegedly failing to meet the enablement requirement. Applicants traverse the rejection and respectfully request reconsideration thereof because one skilled in the art would be able to make and use the claimed invention without being required to perform undue experimentation.

First, the Action alleges that Applicants require substituted benzyl nitriles in the syntheses of the recited compounds and that the invention is not enabled because the public is unaware of how to make substituted benzyl nitriles. Applicants respectfully diagree, and assert that substituted benzyl nitriles are known and used by those of skill in the art. *See* Ong et al., *J.*

Med. Chem. 26: 981-986 (1983), which was cited in the Action. Accordingly, one of skill in the art, armed with Applicants disclosure would be able to make and use the invention as claimed by Applicants.

Second, the Action alleges that the scope of the claimed R^4 substituents is not enabled. The Action bases its allegation on the premise that when R^4 is a nucleophile such as "NR^aR^b, $CH_2NR^aR^b$, SR^a, CH_2OR^a, OR^a, or $C(O)R^c$," it will attack the dichloride, preferentially leading to other products. *See* Office Action at page 7. Applicants respectfully disagree, and assert that when R^a is alkyl and R^a and R^b are joined to form a ring, said substituents are not nucleophiles. Further, when R^a is a nucleophile, one of skill in the art is aware of suitable protecting groups that can be used to prevent such an attack of a dichloride. *See* Green, *Protective Groups in Organic Synthesis*, Wiley-Interscience, New York, (1999).

Third, the Action alleges that the use of Raney nickel necessarily precludes the below substituents recited as R^1, R^2, and R^4 in claims 1-3.

A) $R^4 = (CH_2)_jG(CH_2)_k$ or $G(CH_2)_jG$, where G is oxygen or sulfur, j is 1, 2, 3 or 4, and k is 0, 1 or 2; m is 1, 2 or 3 where at least one R moiety is other than hydrogen; R^a and R^b together are $(CH_2)_jG(CH_2)_k$ or $G(CH_2)_jG$, and n is O, 1, 2 or 3; and SR^a

The Action alleges that sulfur groups will undergo desulfurization when Raney nickel is used, and therefore, the above substituents are not possible. Applicants respectfully disagree, because one of skill in the art would appreciate reducing agents, other than Raney nickel, useful in the syntheses of the claimed compounds, such as for example, lithium aluminum hydride ($LiAlH_4$). *See* March, *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 3rd ed., 815 (1985). Thus, R^4 substituents that contain sulfur are enabled.

B) $R^4 = CN$

The Action alleges that nitriles will be reduced to amines with Raney nickel, and therefore, $R^4 = CN$ is not possible. Applicants respsectfully disagree because one of skill in the art would appreciate that the cyano group could be introduced at a later stage in the synthesis, for example, by direct cyanation of the aromatic ring, or by cyano-de-halogenation, or by other means known in the art. *See* March, *Advanced Organic*

Chemistry: Reactions, Mechanisms, and Structure, 3rd ed., 497, 594 (1985). Thus, R^4 as CN is enabled.

C) $R^4 = C_{2-4}$alkenyl and C_{2-4}alkynyl

The Action alleges that $R^4 = C_{2-4}$alkenyl and C_{2-4}alkynyl, are not possible substituents because said groups will be reduced as is well known in the art. *See* Office Action at page 8. Applicants respectfully disagree because one of skill in the art would appreciate that C_{2-4}alkenyl and C_{2-4}alkynyl groups could also be introduced at a later stage in the synthesis, such as for example, via a *Heck coupling reaction* with aryl bromide in the presence of a paladium catalyst, or other means known in the art. Thus, R^4 as C_{2-4}alkenyl and C_{2-4}alkynyl are enabled.

D) $R^4 = C(O)R^c$ or CO_2R^c

The Action alleges that $R^4 = C(O)R^c$ or CO_2R^c are not possible substituents because they can also be reduced as is well known in the art. *See* Office Action at page 8. Applicants respectfully disagree because one of skill in the art would appreciate that carbonyl groups, such as ketones and aldehydes, can avoid reduction through the use of suitable protecting groups, such as for example, acetals or 1,3-dioxanes. *See* Green, *Protective Groups in Organic Synthesis*, Wiley-Interscience, New York, 279-322 (1999). Further, aryl halides can be converted directly to esters by treatment with nickel carbonyl in ROH solvent. *See* March, *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 3rd ed., 497, 594 (1985). Thus, $R^4 = C(O)R^c$ and CO_2R^c are enabled.

E) R^4 = halogen

The Action alleges that where R^4 is halogen in the ortho position of the phenyl ring, upon reduction of the nitrile an intermolecular cyclization will occur to give spirocyclic indolo-piperidines as taught by Ong et al. *J. Med. Chem.* **1983**, 26, 981-986. *See* Office Action at page 8. Applicants respectfully disagree and direct Examiner's attention to the cited Ong reference, wherein attempts to effect reductive cyclization of 2a with lithium aluminum hydride yielded both a cyclized and non-cyclized product. *See* Ong et al., at page 981. The Ong reference further reports recrystallization of the crude non-cyclized product. *See* Ong et al., at 984. Accordingly, one of skill in the art would

be able to prepare the non-cyclized product when R^4 is halogen in the ortho position of the phenyl ring; thereby enabling said substituent.

F) R^2 is other than H

The Action alleges that where R^2 is other than H, there is no guidance on how to make the recited compounds. *See* Office Action at page 8. Applicants respectfully disagree, and assert that alkylation methods for amines are well known in the art. *See* March, *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure*, 3rd ed., 364 (1985). Thus, compounds where R^2 is other than H are enabled.

G) R^1 substituents

Applicants thank Examiner for directing Applicants' attention to the allowable subject matter. The substituents for R^1 have been amended accordingly.

In light of the foregoing discussion, Applicants respectfully assert that Claims 1-7 meet the enablement requirement of 35 U.S.C. § 112, first paragraph, and request the claim rejection be withdrawn.

Claims 8-10

Claims 8-10 have been rejected under 35 U.S.C. § 112, first paragraph, for failing to meet the enablement requirement. Claim 9 has been canceled herein, rendering its rejection moot.

In regards to Claims 8 and 10, the Action bases its rejection on the premise that the only information given as to what these compounds may do is in terms of K_i and IC_{50} values, and that one cannot predict *a priori* what the outcome of such complex pharmacological behavior would be in the complex diseases of Claim 10. Applicants traverse the rejection and respectfully request reconsideration thereof because the Office has not established a *prima facie* case of non-enablement.

It is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with ***acceptable*** evidence or reasoning which is inconsistent with

the contested statement. (emphasis added). Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure. *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). Without a reason to doubt the objective truth of the statements contained in the specification, the statements contained therein must be relied on for enabling support. *See* MPEP § 2164.04.

The Office has failed to set forth any reasoning or evidence to support the rejection or provided any ***objective*** evidence of non-enablement. (emphasis added). Accordingly, the Office has not established a *prima facie* case of non-enablement. Failing to do so, the burden has not properly shifted to Applicants.

In light of the foregoing discussion, Applicants respectfully assert that Claims 8 and 10 meet the enablement requirement of 35 U.S.C. § 112, first paragraph, and request the claim rejection be withdrawn

IV. The Claimed Invention is Not Indefinite

Claims 1, 7, 8, and 9 have been rejected under 35 U.S.C. § 112, first paragraph, for failing to comply with the written description requirement. Claim 9 has been canceled herein, rendering its rejection moot.

The Action alleges that the application gives no guidance as to what in vivo hydrolysable precursors of the recited compounds are. Although Applicants respectfully disagree with the allegation, in order to expedite prosecution and without disclaimer of subject matter, the claims have been amended accordingly.

V. Conclusion

In view of the foregoing, Applicants respectfully submit that the claims are in condition for allowance. An early notice of the same is earnestly solicited. The Examiner is invited to contact Applicants' undersigned representative at (610) 640-7859 if there are any questions regarding Applicants' claimed invention.

The Commissioner is hereby authorized to debit any underpayment of fee due or credit any overpayment to deposit account 50-0436.

Respectfully submitted,

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